(FILE 'USPAT' ENTERED AT 06:43:08 ON 01 JUL 1999)
L1 506 S POLYPEPTIDE#(5A)GROWTH(2W)FACTOR#
L2 14 S L1 AND 623/CLAS
L3 2 S L2 AND (ALLOGRAFT# OR XENOGRAFT#)

2. 5,569,462, Oct. 29, 1996, Methods for enhancing vascularization of implant devices; Laura A. Martinson, et al., 424/424, 423; 514/964; 604/890.1, 892.1; **623/11** [IMAGE AVAILABLE]

US PAT NO: 5,569,462 [IMAGE AVAILABLE] L3: 2 of 2
US-CL-CURRENT: 424/424, 423; 514/964; 604/890.1, 892.1; **623/11**

DRAWING DESC:

DRWD(2)

FIG. 1 is a bar graph showing the mean host response scores and the mean tissue survival scores for **xenografts** in rats after administration of cyclosporine A for three weeks.

DRAWING DESC:

DRWD(3)

FIG. 2 is a bar graph comparing the mean number of close vascular structures for **xenografts** after daily administration of cyclosporine A for three weeks to the mean number for **xenografts** after daily administration of cyclosporine A for three weeks followed by no cyclosporine A for three weeks.

DETDESC:

DETD(12)

A therapeutic substance may be any molecule having a salutary effect upon a medical condition or useful for a diagnostic purpose in a patient. A therapeutic substance may be a low molecular weight compound such as dopamine for treatment of Parkinson's disease, or a macromolecule such as a polypeptide. Such **polypeptides** may include, for example, hormones, **growth factors**, or enzymes in specific biosynthetic pathways. Production of a therapeutic substance may be an intrinsic property of cells of the device, as with pancreatic islet cells producing insulin. Alternatively, production of a therapeutic substance may be conferred by an extrinsic nucleic acid construct.

DETDESC:

DETD(35)

Histological examination of xenografted cells and host tissue surrounding the **xenografts** showed that encapsulated xenogeneic cells from Group I (no CSA) animals were rejected by 21 days after implantation (Table 2). The **xenografts** were surrounded by a severe host inflammatory response, and the implanted xenogeneic lung tissue was destroyed. **Xenografts** from animals treated with 5 mg CSA/kg (Group

II) were surround by a strong host immune response. Limited survival of fibroblasts and epithelial cells was observed microscopically in Group II xenogeneic cells.

DETDESC:

DETD(37)

Xenografts appeared to be well vascularized after 3 weeks in the presence of 15 mg/kg or more of CSA, as shown by the number of close vascular structures. **Xenografts** at 15 and 30 mg CSA/kg had an average of 129 and 107 close vascular structures per apparatus, respectively (Table 2). The dramatic increase in the number of close vascular structures at 15 and 30 mg CSA/kg compared to 0 mg CSA/kg indicates that CSA is very effective at facilitating neovascularization of xenogeneic cells in an implanted device. The mean number of **xenograft** close vascular structures from Table 2 is shown graphically in FIG. 2 (stippled bars).

DETDESC:

DETD(38)

TABLE 2

Histological Scores of **Xenograft** Apparatuses
(Mean and raw scores)

Tissue Evaluated	Cyclosporine A Dose: 0 mg/kg Raw Scores	0 mg/kg Mean Scores	5 mg/kg Raw Scores	5 mg/kg Mean Scores	15 mg/kg Raw Scores	15 mg/kg Mean Scores	30 mg/kg Raw Scores	30 mg/kg Mean Scores
Host reaction								
3 week	5.5;6;6	5.8	5.5;5;5	5.2	1.5;2;2	1.8	1.5;2;2	1.8
6 week	4;5;5	4.7	5;5;5	5.0	6;6;6	6.0	6;6;6	6.0
Xenogeneic cells								
3 week	2.5;2;2	2.2	3;3;4	3.3	5.5;5;5	5.2	5.5;5;5	5.2
6 week	1.5;2;1	1.5	3.5;4;1	2.8	1.5;2;2	1.8	2;2;2	2.0
Close vascular structures								
3 week	3;0;0							

1.0 12;6;2
6.7 148;123;116
129 118;104;100
107

6 week 2;0;1
1.0 0;0;6
2.0 0;2;0 0.7 2;3;4 3.0

DETDESC:

DETD(41)

Xenogeneic cells had poor survival levels when **xenografts** remained in animals for an additional three weeks after cessation of CSA treatment (Table 2). Such **xenografts** from Group III and Group IV animals became surrounded by a severe host inflammatory response, and the xenogeneic tissue within the device was destroyed. Few close vascular structures were observed in the vicinity of the implants (Table 2, supra). In addition, the inflammatory response of the host was so strong that host tissue adjacent to the outside of the device was damaged. The increased vascularization observed after 3 weeks of CSA treatment may have been responsible for the vigor of the host immune response. When CSA administration was halted, the vasculature may have allowed rapid influx of host immune system cells. The resulting immune response, in turn, may have caused the disappearance of blood vessels near the **xenografts**, since none of the Group III or IV **xenografts** had significantly more close vascular structures than Group I **xenografts**.

DETDESC:

DETD(42)

Two of the 3 **xenografts** from Group II had higher scores for xenogeneic tissue survival compared to **xenografts** from Group III and Group IV (Table 2). Fibroblasts with patches of epithelial tissue were observed in these 2 **xenografts**. All 3 **xenografts** were surrounded by a strong host cellular immune response. However, the size and density of the response was much less than the host response to **xenografts** from Groups III and IV. None of the **xenografts** from Group II animals had close vascular structures at 6 weeks, as shown in Table 2 and in FIG. 2 (dark bars). These results indicate that, under these conditions, immunosuppression with CSA for 3 weeks does not continue after CSA administration is halted.

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US PAT NO: 5,147,400 [IMAGE AVAILABLE] L2: 9 of 14
US-CL-CURRENT: **623/13, 1, 11, 66**

DETDESC:

DETD(32)

Additionally, **polypeptides** such as Human **Growth Factor** (HGF) can also be coated upon or impregnated in the prosthesis to promote healing. The term "Human Growth Factor" or "HGF" embraces those materials, known in the literature, which are referred to as such and includes their biologically active, closely related derivatives. The HGFs can be derived from naturally occurring sources and are preferably produced by recombinant DNA techniques. Specifically, any of the HGFs which are mitogenically active and as such effective in stimulating, accelerating, potentiating or otherwise enhancing the wound healing process are useful herein, e.g., hEGF (urogastrone), TGF-beta, IGF, PDGD, FGF, etc. These and other useful HGFs and closely related HGF derivatives, methods by which they can be obtained and methods and compositions featuring the use of HGFs to enhance wound healing are variously disclosed, inter alia. in U.S. Pat. Nos. 3,883,497; 3,917,824; 3,948,875; 4,338,397; 4,418,691; 4,528,186, 4,621,052; 4,743,679 and 4,717,717; European Patent Applications 0 046 039; 0 128 733; 0 131 868; 0 136 490; 0 147 178; 0 150 572; 0 177 915 and 0 267 015; PCT International Applications WO 83/04030; WO 85/00369; WO 85/01284 and WO 86/02271 and UK Patent Applications GB 2 092 155 A; 2,162,851 A and GB 2 172 890 A, all of which are incorporated by reference herein. Of the known HGFs, hEGF, TGF-beta and IGF are preferred for use in the therapeutic composition of this invention.